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Prevalence, Duration and Severity of Parkinson's Disease in Germany: A Combined Meta-Analysis from Literature Data and Outpatient Samples

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Keywords
Advanced Parkinson's disease · Prevalence · Germany · Meta-analysis

Abstract
Background: Epidemiological data on the prevalence of Parkinson's disease (PD) in Germany are limited. The aims of this study were to estimate the age- and gender-specific prevalence of PD in Germany as well as the severity and illness duration. ***Summary:*** A systematic literature search was performed in 5 different databases. European studies were included if they reported age- and gender-specific numbers of prevalence rates of PD. Meta-analytic approaches were applied to derive age- and gender-specific pooled prevalence estimates. Data of 4 German outpatient samples were incorporated to calculate the proportion of patients with PD in Germany grouped by Hoehn and Yahr (HY) stages and disease duration. In the German population, 178,169 cases of PD were estimated (prevalence: 217.22/100,000). The estimated relative illness duration was 40% with less than 5 years, 31% with 5–9 years, and 29% with more than 9 years. The proportions for different HY stages were estimated at 13% (I), 30% (II), 35% (III), 17% (IV), and 4% (V), respectively. ***Key Message:*** We provide an up-to-date estimation of age- and gender-specific as well as severity-based prevalence figures for PD in Germany. Further community studies are needed to estimate population-based severity distributions and distributions of non-motor symptoms in PD.

Introduction

Parkinson's disease (PD), as the second most common neurodegenerative disorder [1], is clinically not only characterized by its hallmark of motor symptoms, but also by a range of non-motor symptoms including autonomic, cognitive, affective, and behavioral manifestations [2, 3]. The non-motor symptoms of PD have been shown to contribute to increased disability and suffering, poorer prognosis, and quality of life decrements of patients and their families as well as PDs considerable economic burden [4, 5].

Although crude epidemiological information about PD exist for Germany, the number of solid state-of-the-art prevalence studies in Germany is very limited and findings can hardly be generalized to the entire population [6]. More precisely, we identified only 4 studies from the early 1990s [6–9], which are methodologically hetero-

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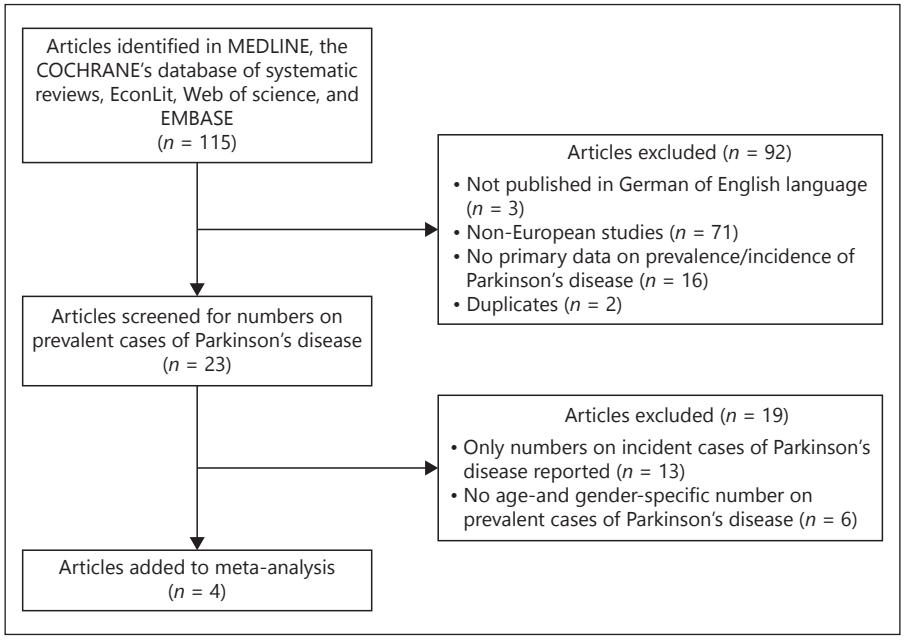

Fig. 1. Added studies from the literature update after 2004.

geneous, limited in its scope and detail and provide highly variable results [10]. Thus, it is difficult to estimate the disease burden caused by PD as well as to specify what proportion of the population is affected by different degrees of severity and the degree of met and unmet needs for diagnosis and treatment. The lack of appropriate and detailed epidemiological data is a particular barrier for rational planning and the allocation of resources as well as for prioritizing research policies. In the case of PD as a chronic progressive disorder [11, 12], this is related particularly to the yet unmet need for reliable epidemiological figures including distributions of severity stages or disease duration.

A widely used measure of the severity of PD is the Hoehn and Yahr (HY) rating scale, which provides a crude but clinically meaningful symptom-based measure of the disease progression [13]. Unfortunately, only a few European and none of the German studies has reported prevalence estimates of PD stratified according to HY stages or disease duration [10].

This study makes an attempt to fill this important gap of knowledge by providing prevalence estimates of PD by HY stages and disease duration using a mixed method approach. Using a meta-analytic approach of European epidemiological studies, we first provide consolidated age- and gender-specific prevalence estimates of PD in Germany. Then, we link the estimated age- and gender-specific prevalence with appropriate German databases containing information on clinically well-defined outpatients with PD to provide estimates of the prevalence pattern of PD by HY stages and illness duration.

Methods

Based on a systematic literature review of European studies to identify relevant data sources, we first pooled the available study data separately by age and gender to derive prevalence estimates of PD by age and gender. In the second step, these prevalence data were then transformed into 'number of persons affected' by using the respective age- and gender-specific population registry data for Germany as of December 31, 2013. In the third step, we standardized available data by age and gender from 4 German samples of outpatients with PD that have provided information about HY stages and illness duration by age and gender using the expected population of patients with PD in Germany as the reference population. These standardized relative frequencies were then used to compute a pooled estimate. Details of the study methods are described below.

Data Sources and Data Extraction

The primary source for the literature data was a systematic review by von Campenhausen et al. [10] that included studies based on primary data reporting the prevalence and incidence of PD in Europe from 1966 until 2004. The systematic review comprised 44 studies estimating prevalence or incidence rates of PD of which 21 studies reported age- and gender-specific prevalence as well as the size of the underlying population [14–34]. To supplement these data by studies that were published after 2004, an additional systematic literature search was performed using the same search strategy as described by von Campenhausen et al. [10] (Fig. 1). Four studies which provided data on age- and gender-specific

Table 1. Outpatient samples of patients with PD providing data on duration and severity of disease

Sample	Number of patients	Recruitment criteria	Reference
GEPAD	1,449	Random sample of patients recruited between September and October 2005 from a representative sample of 315 office-based neurologists in Germany	Riedel et al. [5], 2008; Riedel et al. [50], 2010; Riedel et al. [51], 2010
KNP	145	Patients from North Hessia recruited between the first and second quarter of 2000 by an outpatient department for movement disorders, a specialized PD clinic, 2 office-based neurologists, and 12 general practitioners	Spottke et al. [52], 2005
NeuroPa	425	Patients of 12 specialized office-based neurologists in Berlin recruited in the fourth quarter of 2006	Ehret et al. [7], 2009
QUANUP	234	Random sample of patients of 21 office-based neurologists	Unpublished data

PD, Parkinson's disease.

prevalence were additionally included [35–38]. Thus, 25 studies were eligible for further analyses.

From each study, age- and gender-specific numbers were extracted by 2 independent reviewers. Study design, country, and quality of the studies were determined. Following the recommendations proposed by von Campenhausen et al. [10], a study was called a high quality study, if an established diagnostic criterion was used to identify cases of PD and the screening was conducted by neurologists [10].

Information on the distribution of the duration and severity of disease among patients with PD in Germany was obtained from 4 outpatient samples (Table 1). In each sample, the duration of the disease was measured as the time from beginning of the symptoms until the examination date, categorized into <5, 5–9, and >9 years. The disease severity was assessed using the 5 stages of the HY scale [13].

Statistical Analyses

Findings from eligible studies were extracted and pooled prevalence estimates with 95% CI were computed for each age and gender category from the individual studies. Age- and gender-specific prevalence estimates were calculated for all studies providing numbers for the specific age and gender category. These estimates were transformed using the Freeman-Tukey double arcsine function to stabilize their variances [39]. A pooled prevalence with a 95%-CI was calculated assuming a random effects model for the transformed prevalence, because there was indication of heterogeneity in most of the age and gender categories. The pooled prevalence was transformed back using the inverse of the Freeman-Tukey double arcsine function. This function requires the specification of a sample size for the pooled prevalence, which was assumed to be the sum of the individual study populations [40].

The expected number of cases with PD in Germany was calculated by multiplying age- and gender-specific population counts of the German population using the total population registry data for Germany as of December 31, 2013 [41] with the pooled prevalence estimations in the respective age and gender category. Since the existing German studies partly reported prevalence of PD in the population aged 65 years and above, the prevalence of PD in the German population aged 65 years and above was calculated for comparison purposes too. Therefore, the meta-analysis was repeated with studies reporting gender-specific numbers on study population and prevalent cases in at least one of the following age categories: 65–74, 75–84, and ≥85 years.

A meta-analysis was performed to obtain pooled relative frequencies of patients with PD in Germany in categories of disease severity and disease duration based on the 4 outpatient samples:

(i) The relative frequency of patients in the respective category in each outpatient sample was standardized with respect to age and gender using the expected number of cases of PD in Germany as the standard population, since the distribution of age and gender might differ between the selective outpatient samples and the PD population in Germany. In addition, severity and disease duration of PD are likely to be associated with age. Since frequencies might be low for some categories, the variance of the standardized relative frequency was calculated based on the Poisson approximation [42].

(ii) A pooled relative frequency was calculated assuming a random effects model for the standardized relative frequencies across the 4 outpatient samples, since there was no indication of heterogeneity in most of the categories of the duration of PD and the HY stages. Since the sum of the pooled relative frequencies over all categories may not equal one, the relative frequencies were divided by the sum of the pooled relative frequencies for the duration of the disease and the HY stages, respectively.

In each random effects model, the between-study variance was estimated using the method of DerSimonian-Laird [43] and heterogeneity was assessed with the I^2-statistic (a value above 60% indicating heterogeneity) [44].

Results

Prevalence of PD in Germany

Of the 25 studies providing age- and gender-specific prevalence estimates, numbers in at least one of the age categories <50, 50–59, 60–69, 70–79 or ≥80 years could be extracted from 21 studies (Table 2). A total of 10 of these studies were conducted in Italy [16, 17, 19, 23, 24, 26, 28–30, 35], followed by 6 studies in the United Kingdom [27, 31–33, 36, 38]. Notably, none of the studies were conducted in Germany. Of these, 4 were conducted using a door-to-door design [14, 18, 24, 26] and 12 of the studies were cross-sectional based on medical records [16, 19, 22, 25, 27, 31–36, 38], and 3 of the studies were assigned a low quality [22, 31, 38]. The pooled prevalence estimates for all age and gender categories are displayed in Table 3. Using the age and gender distribution of the total German population as of December 31, 2013, 178,169 prevalent cases are expected, corresponding to a prevalence estimate of 217.22/100,000. The age- and gender-specific distributions of the expected prevalent cases of PD are also displayed in Figure 2. Using the lower and upper limits of the CIs for the expected cases of PD in each age and gender category, a lower extreme prevalence estimate of 173.76/100,000 and an upper extreme prevalence estimate of 265.80/100,000 for the total German population are obtained. Using these prevalence estimate, in the German population, 1,829 cases (1.0% of all PD cases) under 50 years, 15,456 cases (8.7%) between 50 and 59 years, 31,754 cases (17.8%) between 60 and 69 years, 72,536 cases (40.7%) between 70 and 79 years, and 56,594 cases (31.8%) greater or equal than 80 years are expected. The expected numbers of prevalent cases by gender were 87,803 men (prevalence 217.62/100,000) and 90,366 women (prevalence 216.84/100,000). Although the prevalence is higher in men than in women across all age categories, the estimated overall prevalence in women and men are similar due to the higher life expectancy and consequently the higher proportion of women in the ages above 70 years.

A sum of 11 studies reported prevalences in at least one of the age categories 65–74, 75–84, and ≥85 years [14–16, 19–21, 24, 27, 32, 36, 37]. Using only these studies in the meta-analysis, a pooled prevalence of 1,078.71/100,000 was estimated for the German population aged 65 years and above.

Duration of PD and Disease Severity

The relative frequencies of the duration of PD and the HY stages as well as the age- and gender-standardized figures with 95% CIs are displayed in Table 4. The standardization generally resulted in small changes concerning the duration of the disease. However, throughout all samples, the relative frequencies of the HY stages I and II was decreased and the relative frequency of the HY stage V was increased after the standardization.

The pooled estimates of the relative disease duration of PD was as follows: 0.40 95% CI (0.27–0.52) with less than 5 years, 0.31 95% CI (0.28–0.34) with 5–9 years, and 0.29 95% CI (0.19–0.40) with more than 9 years. The pooled estimates of the relative frequency of the HY-stages were as follows: 0.13 95% CI (0.10–0.17) at stage I, 0.30 95% CI (0.27–0.33) at stage II, 0.35 95% CI (0.25–0.46) at stage III, 0.17 95% CI (0.15, 0.20) at stage IV, and 0.04 95% CI (0.01, 0.06) at stage V.

Discussion

Given the need for clinically detailed data about the number of PD cases in Germany by duration and severity and being aware that it is unlikely that such a major epidemiological study program will become reality in the near future, we applied a meta-analytic approach to provide such crucial information as a time- and cost-efficient alternative. Our age- and gender-specific estimates of the prevalence of PD in Germany are more detailed and comprehensive as estimates provided by the single studies conducted in Germany so far and can be seen as being most likely a more accurate reflection of the true prevalence and the true number of cases affected. Our additional stratification by disease severity and duration adds to the clinical relevance and utility. Neither the exclusion of individual studies nor the restriction to high quality studies had a high impact on the pooled prevalence estimates (data available at request).

Referring to the total German population as of December 31, 2013, we estimated a total prevalence of PD in Germany of 217.22/100,000 with a range of uncertainty between 173.76 and 265.80/100,000. For the population aged 65 years and above, a prevalence of 1,078.71/100,000 was estimated. This findings agree relatively well with 2 German high-quality, cross-sectional studies conducted by Vieregge et al. [6] and Trenkwalder et al. [9] that reported prevalence estimates of 183/100,000 in a rural-urban area of Northern Germany and 713/100,000 in patients over the age of 65 years in a rural area of Bavaria. Our estimates were slightly higher but were in a similar order of magnitude. Our results are further in agreement with a recently conducted study based on claims data from German health insurances, which estimated the

Table 2. Studies included in the meta-analysis

Study	Country	Design	Quality*	Population size	Prevalent men (number of men in the study)/prevalent women (number of women in the study)				
					<50 years	50–59 years	60–69 years	70–79 years	≥80 years
Benito-Leon, et al. [14]	Spain	Door-to-Door	High	5,278				28 (1,024)/ 13 (1,342)	8 (475)/ 24 (786)
Casetta, et al. [16]	Italy	Cross-sectional	High	38,360	2 (12,966)/ 1 (12,549)	1 (2,539)/ 1 (2,674)	5 (1,826)/ 8 (2,151)		
Chio, et al. [17]	Italy	Consumption	High	61,830	0 (18,672)/ 0 (17,946)	6 (4,200)/ 4 (4,476)	16 (3,710)/ 8 (4,617)	22 (2,004)/ 21 (3,145)	11 (912)/ 16 (2,108)
Claveria, et al. [18]	Spain	Door-to-Door	High	3,503		0 (181)/ 0 (205)	1 (240)/ 2 (239)	3 (149)/ 1 (169)	7 (43)/ 6 (99)
D'Alessandro, et al. [19]	Italy	Cross-sectional	High	22,322			4 (944)/ 5 (980)	11 (600)/ 10 (773)	1 (206)/ 2 (339)
Errea, et al. [22]	Spain	Cross-sectional	Low	60,724	0 (18,647)/ 2 (17,026)	4 (3502)/ 3 (3,487)	21 (4,442)/ 17 (4,282)	29 (2,633)/ 28 (3,346)	16 (1,339)/ 14 (2,021)
Granieri, et al. [23]	Italy	Longitudinal	High	176,621		23 (12,979)/ 29 (14,859)	43 (9,444)/ 38 (11,787)	53 (5,927)/ 38 (8,702)	
Kis, et al. [24]	Italy	Door-to-Door	High	750			2 (173)/ 1 (238)	4 (127)/ 4 (147)	
Marttila and Rinne [25]	Finland	Cross-sectional	High	402,988	8 (150,180)/ 5 (151,667)	27 (19,824)/ 27 (25,592)	88 (17,478)/ 121 (24,283)	56 (7,608)/ 116 (13,988)	8 (1,721)/ 28 (4,342)
Morgante, et al. [26]	Italy	Door-to-Door	High	19,955	0 (9,007)/ 0 (8,707)	2 (1,261)/ 1 (1,335)	6 (969)/ 7 (1,123)	12 (708)/19 (859)	7 (214)/ 9 (314)
Morgante, et al. [35]	Italy	Cross-sectional	High	13,431	0 (4,710)/ 0 (4,361)	1 (780)/ 1 (736)	1 (710)/ 1 (723)	3 (417)/ 3 (572)	2 (153)/ 2 (269)
Mutch, et al. [27]	United Kingdom	Cross-sectional	High	151,616		9 (8,983)/ 6 (10,336)	26 (7,204)/ 16 (9,332)	51 (4,536)/ 54 (7,969)	16 (1,069)/ 63 (3,036)
Porter, et al. [36]	United Kingdom	Cross-sectional	High	108,597	1 (34,381)/ 0 (35,715)	5 (6,921)/ 3 (7,045)	16 (5,316)/ 17 (5,816)	38 (3,880)/ 44 (5,219)	14 (1,408)/ 23 (2,896)
Rosati, et al. [28]	Italy	Longitudinal	High	397,891		34 (17,259)/ 36 (17,789)	55 (16,576)/ 52 (17,499)	50 (8,557)/ 40 (10,857)	
Rosati, et al. [30]	Italy	Longitudinal	High	273,421		28 (10,753)/ 21 (11,959)	44 (11,120)/ 37 (12,231)	21 (6,610)/ 14 (7,701)	
Rosati, et al. [29]	Italy	Longitudinal	High	1,473,800		144 (61,776)/ 113 (63,878)	225 (58,185)/ 184 (61,374)	121 (29,788)/ 87 (37,037)	
Schrag, et al. [31]	United Kingdom	Cross-sectional	Low	121,608	4 (44,848)/ 0 (46,140)	9 (6,207)/ 4 (5,714)	19 (4,289)/ 10 (4,184)	29 (2,810)/ 32 (3,540)	21 (1,266)/ 28 (2,607)
Sutcliffe, et al. [33]	United Kingdom	Cross-sectional	High	208,499	2 (66,667)/ 2 (66,667)	10 (10,870)/ 4 (11,111)	26 (9,155)/ 27 (10,000)	46 (5,436)/ 47 (7,781)	21 (1,624)/ 41 (3,832)
Sutcliffe and Meara [32]	United Kingdom	Cross-sectional	High	302,500		21 (15,589)/ 7 (14,710)	40 (12,994)/ 29 (14,474)	89 (8,803)/ 63 (11,495)	50 (3,200)/ 81 (7,300)
Taba and Asser [34]	Estonia	Cross-sectional	High	153,240	2 (53,132)/ 2 (53,092)	10 (7,683)/ 12 (9,662)	25 (6,267)/ 52 (9,367)	35 (2,813)/ 78 (6,356)	16 (1,244)/ 38 (3,624)
Wickremaratchi et al. [38]	United Kingdom	Cross-sectional	Low	292,637	4 (106,487)/ 1 (101,006)	14 (16,901)/ 10 (15,348)	38 (11,616)/ 25 (11,539)	68 (8,193)/ 61 (9,288)	74 (4,413)/ 85 (7,846)

* A high quality study must report the use of an established diagnostic criterion to identify cases of PD and a screening of cases of PD by neurologists.

Table 3. Expected patients with PD in the German population

Age, years	Gender	German population	Pooled prevalence of PD/ 100,000 (95% CI)	Expected cases of PD (95% CI)
<50	Male	24,375,140	4.86 (3.13–6.99)	1,185 (763–1,697)
	Female	23,323,134	2.76 (1.49–4.41)	644 (348–1,029)
50–59	Male	6,156,469	146.46 (116.98–179.24)	9,017 (7,202–11,035)
	Female	6,102,406	105.52 (77.34–138.05)	6,439 (4,720–8,424)
60–69	Male	4,401,202	385.76 (352.87–420.09)	16,978 (15,531–18,489)
	Female	4,652,554	317.58 (266.21–373.46)	14,776 (12,386–17,375)
70–79	Male	3,876,835	1,001.77 (803.89–1,221.15)	38,837 (31,165–47,342)
	Female	4,668,244	721.88 (555.03–910.43)	33,699 (25,910–42,501)
≥80	Male	1,537,207	1,417.22 (1,103.10–1,769.94)	21,786 (16,957–27,208)
	Female	2,927,387	1,189.03 (940.73–1,465.96)	34,808 (27,539–42,914)
All ages	Male	40,346,853		87,803
	Female	41,673,725		90,366
	Both	82,020,578		178,169

PD, Parkinson's disease.

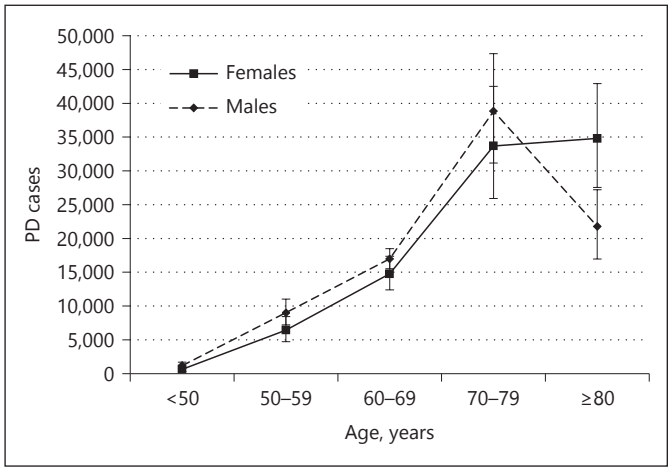

Fig. 2. Expected cases of Parkinson's disease (PD) in Germany by age and gender.

prevalence in the German population aged 65 years and older as 1,680/100,000. Although this study had a large sample size and covers all regions of Germany, the comparability with our results is somewhat limited due to general differences between primary and secondary data sources (e.g., case ascertainment) [45].

The results of our meta-analysis further suggest 3 other noteworthy findings. (i) The age-specific prevalence of PD in men is moderately higher than in women. There is growing data on biological reasons for gender differences in PD [46, 47] but they are not yet fully understood. (ii) PD prevalence is considerably age dependent. The prevalence ranges from 3.82/100,000 in the youngest age group (below 50 years) to 1,273.58/100,000 in the age group above 80 years. (iii) There were enough studies to estimate the prevalence of PD in the population younger than 60 years. Further analyses of the age groups <50 years and 50–59 years indicated that the prevalence of PD in these age groups might be decreasing since the 1980s and differ between countries (we compared United Kingdom and Italy only because all other countries provided at most 1 study for these age groups), although the small number of events in these age groups precludes statistically secured conclusions (Table 5).

Community surveys as a variant of general population survey ("door-to-door") studies are assumed to be the gold standard for prevalence estimation, since these studies detect cases that would not have been recognized in other study designs, for example, in cross-sectional studies. However, the identified door-to-door studies have relatively small sample sizes and numbers of cases, leading to increased uncertainty in the prevalence estimation. In this meta-analysis, only 4 door-to-door studies could be included precluding a restriction to door-to-door studies. Nevertheless, a limitation of this meta-analysis is that the prevalence estimates for PD in Germany were mostly based on data from cross-sectional studies based on medical records and might therefore lead to an underestimation.

Table 4. Relative frequencies and standardized relative frequencies for the duration of the disease and HY stages in the 4 outpatient samples of patients with PD

	QUANUP (n = 234)			KNP (n = 145)			NeuroPa (n = 425)			GEPAD (n = 1,449)		
	n	relative frequency	standard relative frequency (95% CI)	n	relative frequency	standard relative frequency (95% CI)	n	relative frequency	standard relative frequency (95% CI)	n	relative frequency	standard relative frequency (95% CI)
Duration of PD, years	224*			142*			409*			1,372*		
<5	70	0.31	0.36 (0.25–0.46)	50	0.35	0.25 (0.18–0.33)	179	0.44	0.40 (0.33–0.47)	680	0.50	0.51 (0.47–0.56)
5–9	82	0.37	0.33 (0.25–0.41)	39	0.27	0.34 (0.12–0.56)	121	0.30	0.28 (0.22–0.34)	425	0.31	0.30 (0.27–0.34)
≥10	72	0.32	0.31 (0.22–0.40)	53	0.37	0.41 (0.18–0.65)	109	0.28	0.32 (0.25–0.39)	267	0.19	0.18 (0.16–0.21)
HY stages	223**			145**			300**			1,396**		
I	49	0.22	0.20 (0.13–0.27)	19	0.13	0.10 (0.05–0.15)	36	0.12	0.10 (0.06–0.14)	201	0.14	0.13 (0.11–0.15)
II	83	0.37	0.35 (0.25–0.44)	43	0.30	0.25 (0.16–0.33)	84	0.28	0.26 (0.19–0.32)	416	0.30	0.29 (0.25–0.32)
III	49	0.22	0.29 (0.19–0.39)	44	0.30	0.21 (0.14–0.28)	131	0.44	0.44 (0.35–0.53)	540	0.39	0.38 (0.34–0.42)
IV	38	0.17	0.15 (0.09–0.20)	25	0.17	0.16 (0.08–0.24)	38	0.13	0.14 (0.09–0.19)	211	0.15	0.17 (0.14–0.20)
V	4	0.02	0.02 (0.00–0.04)	14	0.10	0.28 (0.05–0.52)	11	0.04	0.06 (0.02–0.10)	28	0.02	0.03 (0.02–0.05)

PD, Parkinson's disease. Patients with missing information on duration of PD (*) or HY stages (**) were excluded from the respective analysis

Our study underlies the assumption that the prevalence of PD is comparable between European countries. A further limitation is thus the lack of diversity in the countries providing prevalence estimates. The prevalence of PD might differ between countries, for example, because of environmental factors and life expectancy. Since mainly Italy, Spain, and the United Kingdom were providing age- and gender-specific prevalence estimates, a pattern in the prevalence across the European countries could not be identified and it remained unclear if an extrapolation to Germany is valid. Unfortunately, PD prevalence estimates in the included studies of the meta-analysis were mostly reported only stratified by age and gender. This precludes the investigation of other risk factors of PD prevalence besides age and gender.

Using 4 outpatient samples, we also determined PD patient proportions for duration groups and HY severity stages. Consistent with the chronic progressive character of PD, we estimated that the disease duration was relatively long, that is, more than 10 years, in 29% of the PD patients. However, information on disease duration was obtained from patient records and may therefore be inaccurate due to patient-reported onset dates. Nevertheless, given accurate records of disease duration, we estimated that about at least one-third of the PD patients survive more than 10 years. By comparing these proportions with the distribution of the HY stages, we concluded that a non-negligible number of patients are long-term survivors with a slow progression of the disease and thus may not reach the highly disabling late stage PD (defined as HY stages IV and V) [48, 49]. External data to validate the distribution of the duration of the disease is missing in the literature.

In our study, we estimated a low disease severity (HY stage I or II) in 43% of the PD patients. This proportion is smaller than in most of the studies identified by the review of von Campenhausen et al. [10]. Of the 5 studies that reported relative frequencies of the HY stages, 4 studies classified 55% and 1 study classified 27% of the patients in HY stages I or II. However, since the distribution differed substantially between the 5 studies, a comparison of the studies is not feasible.

Furthermore, a trend in age toward more severe HY stages for older age groups was observed in the outpatient samples. In each age category, male patients were on average at slightly higher stages of the disease than women (data available at request). As a consequence, the relative frequency of the HY stages I and II was lower and the HY stage V was higher after the standardization in all outpatient samples. A limitation of this analysis was that the

Table 5. Pooled prevalences for the population younger than 60 years stratified by year and country

	Pooled prevalence of PD/100,000 (95% CI)			
	age <50 years		age 50–59 years	
	males	females	males	females
Year of the studies				
Before 1990	5.44 (2.89–8.81)	3.92 (1.82–6.83)	166 (124–213)	126 (86–173)
From 1990 until 2000	4.81 (1,69–9.53)	3.34 (0.40–9.11)	141 (105–182)	82 (56–114)
After 2000	4.25 (1.56–8.26)	1.31 (0.10–3.88)	87 (54–130)	65 (36–102)
Country of study				
Italy	5.36 (0.57–15.0)	4.19 (0.44–15.9)	207 (172–245)	176 (152–203)
United Kingdom	4.92 (2.56–8.03)	1.58 (0.41–3.52)	107 (83–133)	57 (40–77)

PD, Parkinson's disease.

outpatient samples are not representative for the German population of patients with PD for other reasons than age or gender. For instance, patients living in nursing homes or severely affected patients not able to visit an office-based physician are under-represented in all considered outpatient samples.

Conclusion

We contributed to the current description of the epidemiology of PD in Germany by providing up-to-date age- and gender-specific as well as severity-based prevalence figures. Such figures are urgently needed for planning resource allocation and assessing the disease burden. For instance, the calculation of the proportion of patients with late-stage PD can often only roughly be estimated due to the lack of HY- and duration-specific epidemiological studies. However, the validity of the prevalence figures remains unclear, since they are mainly based on cross-sectional studies from few European countries and selective patient samples in Germany. Therefore, high quality studies determining population-based figures on the distribution of severity figures and non-motor symptoms of PD are recommended to face the increasing demand of health services for the oldest and most severely disabled patients on a rational basis.

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Disclosure Statement

D.E. and O.R. are working for an institute that occasionally performs studies for pharmaceutical industries. These companies include Bayer, Celgene, GlaxoSmithKline, Mundipharma, Novartis, Sanofi-Aventis, Sanofi Pasteur MDS, and STADA. S.-C.S. and B.W. are employees of AbbVie Deutschland GmbH& Co. KG. M.B.-G., R.D.,H.-U.W., and J.-P.R. declare no conflicts of interest.

References

1 de Lau LM, Breteler MM: Epidemiology of Parkinson's disease. Lancet Neurol 2006;5:525–535.

2 Lees AJ, Hardy J, Revesz T: Parkinson's disease. Lancet 2009;373:2055–2066.

3 Wirdefeldt K, Adami HO, Cole P, Trichopoulos D, Mandel J: Epidemiology and etiology of Parkinson's disease: a review of the evidence. Eur J Epidemiol 2011;26(suppl 1):S1–S58.

4 Brewster M, Bondi CD, Khairnar R, Kamal KM, Pawar GV: A systematic review of quality of life and caregiver burden in Parkinson's disease. Value Health 2013;18:467–486.

5 Riedel O, Klotsche J, Spottke A, et al: Cognitive impairment in 873 patients with idiopathic Parkinson's disease. Results from the German study on epidemiology of Parkinson's disease with dementia (GEPAD). J Neurol 2008;255:255–264.

6 Vieregge P, Kleinhenz J, Fassl H, Jorg J, Kompf D: Epidemiology and out-patient care in Parkinson's disease – results from a pilot-study in northern Germany (Schleswig-Holstein). J Neural Transm Suppl 1991;33:115–118.

7 Ehret R, Balzer-Geldsetzer M, Reese JP, et al: [Direct costs for Parkinson's treatment in private neurology practices in Berlin]. Nervenarzt 2009;80:452–458.

8 Evers S, Obladen M: [Epidemiology and therapy of Parkinson disease in inpatient nursing homes]. Z Gerontol 1994;27:270–275.

9 Trenkwalder C, Schwarz J, Gebhard J, et al: Starnberg trial on epidemiology of Parkinsonism and hypertension in the elderly. Prevalence of Parkinson's disease and related disorders assessed by a door-to-door survey of inhabitants older than 65 years. Arch Neurol 1995;52:1017–1022.
10 von Campenhausen S, Bornschein B, Wick R, et al: Prevalence and incidence of Parkinson's disease in Europe. Eur Neuropsychopharmacol 2005;15:473–490.
11 Volkmann J, Albanese A, Antonini A, et al: Selecting deep brain stimulation or infusion therapies in advanced Parkinson's disease: an evidence-based review. J Neurol 2013;260:2701–2714.
12 Winter Y, Balzer-Geldsetzer M, von Campenhausen S, et al: Trends in resource utilization for Parkinson's disease in Germany. J Neurol Sci 2010;294:18–22.
13 Hoehn MM, Yahr MD: Parkinsonism: onset, progression and mortality. Neurology 1967;17:427–442.
14 Benito-Leon J, Bermejo-Pareja F, Rodriguez J, Molina JA, Gabriel R, Morales JM: Prevalence of PD and other types of Parkinsonism in three elderly populations of central Spain. Mov Disord 2003;18:267–274.
15 Bergareche A, De La Puente E, Lopez de MA, et al: Prevalence of Parkinson's disease and other types of parkinsonism. A door-to-door survey in Bidasoa, Spain. J Neurol 2004;251:340–345.
16 Casetta I, Granieri E, Govoni V, et al.: Epidemiology of Parkinson's disease in Italy. A descriptive survey in the U.S.L. of Cento, province of Ferrara, Emilia-Romagna. Acta Neurol (Napoli) 1990;12:284–291.
17 Chio A, Magnani C, Schiffer D: Prevalence of Parkinson's disease in northwestern Italy: comparison of tracer methodology and clinical ascertainment of cases. Mov Disord 1998;13:400–405.
18 Claveria LE, Duarte J, Sevillano MD, et al: Prevalence of Parkinson's disease in Cantalejo, Spain: a door-to-door survey. Mov Disord 2002;17:242–249.
19 D'Alessandro R, Gamberini G, Granieri E, Benassi G, Naccarato S, Manzaroli D: Prevalence of Parkinson's disease in the republic of San Marino. Neurology 1987;37:1679–1682.
20 de Rijk MC, Breteler MM, Graveland GA, et al: Prevalence of Parkinson's disease in the elderly: the Rotterdam Study. Neurology 1995;45:2143–2146.
21 Dias JA, Felgueiras MM, Sanchez JP, Goncalves JM, Falcao JM, Pimenta ZP: The prevalence of Parkinson's disease in Portugal. A population approach. Eur J Epidemiol 1994;10:763–767.
22 Errea JM, Ara JR, Aibar C, de Pedro-Cuesta J: Prevalence of Parkinson's disease in lower Aragon, Spain. Mov Disord 1999;14:596–604.
23 Granieri E, Carreras M, Casetta I, et al: Parkinson's disease in Ferrara, Italy, 1967 through 1987. Arch Neurol 1991;48:854–857.
24 Kis B, Schrag A, Ben-Shlomo Y, et al: Novel three-stage ascertainment method: Prevalence of PD and Parkinsonism in south Tyrol, Italy. Neurology 2002;58:1820–1825.
25 Marttila RJ, Rinne UK: Epidemiology of Parkinson's disease in Finland. Acta Neurol Scand 1976;53:81–102.
26 Morgante L, Rocca WA, Di Rosa AE, et al: Prevalence of Parkinson's disease and other types of Parkinsonism: a door-to-door survey in three Sicilian municipalities. The Sicilian Neuro-epidemiologic Study (SNES) Group. Neurology 1992;42:1901–1907.
27 Mutch WJ, Dingwall-Fordyce I, Downie AW, Paterson JG, Roy SK: Parkinson's disease in a Scottish city. Br Med J (Clin Res Ed) 1986;292:534–536.
28 Rosati G, Granieri E, Pinna L, et al: Parkinson's disease. Prevalence and incidence in the province of Sassari, north Sardinia. Acta Neurol (Napoli) 1978;33:201–207.
29 Rosati G, Granieri E, Pinna L, et al: The risk of Parkinson disease in mediterranean people. Neurology 1980;30:250–255.
30 Rosati G, Granieri E, Pinna L, Devoto MC: The frequency of Parkinson's disease in the province of Nuoro (Sardinia). Acta Neurol (Napoli) 1979;1:303–308.
31 Schrag A, Ben-Shlomo Y, Quinn NP: Cross sectional prevalence survey of idiopathic Parkinson's disease and Parkinsonism in London. BMJ 2000;321:21–22.
32 Sutcliffe RL, Meara JR: Parkinson's disease epidemiology in the Northampton district, England, 1992. Acta Neurol Scand 1995;92:443–450.
33 Sutcliffe RL, Prior R, Mawby B, McQuillan WJ: Parkinson's disease in the district of the Northampton health authority, United Kingdom. A study of prevalence and disability. Acta Neurol Scand 1985;72:363–379.
34 Taba P, Asser T: Prevalence of Parkinson's disease in Estonia. Acta Neurol Scand 2002;106:276–281.
35 Morgante L, Nicoletti A, Epifanio A, et al: Prevalence of Parkinson's disease and other types of Parkinsonism in the Aeolian Archipelago, Sicily. Parkinsonism Relat Disord 2008;14:572–575.
36 Porter B, Macfarlane R, Unwin N, Walker R: The prevalence of Parkinson's disease in an area of north Tyneside in the north-east of England. Neuroepidemiology 2006;26:156–161.
37 Totaro R, Marini C, Pistoia F, Sacco S, Russo T, Carolei A: Prevalence of Parkinson's disease in the l'Aquila district, central Italy. Acta Neurol Scand 2005;112:24–28.
38 Wickremaratchi MM, Perera D, O'Loghlen C, et al: Prevalence and age of onset of Parkinson's disease in Cardiff: a community based cross sectional study and meta-analysis. J Neurol Neurosurg Psychiatry 2009;80:805–807.
39 Freeman MF, Tukey JW: Transformations related to the angular and the square root. Ann Math Stat 1950;21:607–611.
40 Miller JJ: The inverse of the Freeman-Tukey double arcsine transformation. Am Stat 1978;32:138.
41 Eurostat EC: Population on January 1 by age and sex. http://ec.europa.eu/eurostat/data/database (accessed December 29, 2016).
42 Bains N: Standardization of rates. http://core.apheo.ca/resources/indicators/Standardization report_NamBains_FINALMarch16.pdf (accessed September 26, 2016).
43 DerSimonian R, Laird N: Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–188.
44 Higgins JP, Green S (eds): Cochrane handbook for systematic reviews of interventions, edition 5.1.0. The Cochrane Collaboration, 2011.
45 Riedel O, Bitters D, Amann U, Garbe E, Langner I: Estimating the prevalence of Parkinson's disease (PD) and proportions of patients with associated dementia and depression among the older adults based on secondary claims data. Int J Geriatr Psychiatry 2016;31:938–943.
46 Kotagal V, Albin RL, Muller ML, Koeppe RA, Frey KA, Bohnen NI: Gender differences in cholinergic and dopaminergic deficits in Parkinson disease. J Neural Transm (Vienna) 2013;120:1421–1424.
47 Simunovic F, Yi M, Wang Y, Stephens R, Sonntag KC: Evidence for gender-specific transcriptional profiles of nigral dopamine neurons in Parkinson disease. PLoS One 2010;5:e8856.
48 Coelho M, Ferreira JJ: Late-stage Parkinson disease. Nat Rev Neurol 2012;8:435–442.
49 Coelho M, Marti MJ, Tolosa E, et al: Late-stage Parkinson's disease: the Barcelona and Lisbon cohort. J Neurol 2010;257:1524–1532.
50 Riedel O, Heuser I, Klotsche J, Dodel R, Wittchen HU: Occurrence risk and structure of depression in Parkinson disease with and without dementia: results from the GEPAD study. J Geriatr Psychiatry Neurol 2010;23:27–34.
51 Riedel O, Klotsche J, Spottke A, et al: Frequency of dementia, depression, and other neuropsychiatric symptoms in 1,449 outpatients with Parkinson's disease. J Neurol 2010;257:1073–1082.
52 Spottke AE, Reuter M, Machat O, et al: Cost of illness and its predictors for Parkinson's disease in Germany. Pharmacoeconomics 2005;23:817–836.